Remarks

Claims 23-44, 48, 102-106 and 142-148 are pending in the application. In the action, the Examiner issued new grounds of rejection, rejecting claims 23-44, 48, 102-106 and 142-148 under 35 USC §112, first paragraph as assertedly lacking written description and enablement in the specification. The examiner also provisionally rejected the claims under the doctrine of obviousness-type double patenting over claims 1-53 of application no. 11/088,693, and over claims 1-22 of application no. 10/207,655 in view of Shan (*J Immunol* 162:6589-95, 1999 (hereinafter "Shan") and Liu (*J. Immunol* 139:3521-26, 1987 (hereinafter "Liu").

Applicants respectfully request reconsideration in light of the amendments and response filed herein.

I. The Amendment

Support for the amendment to claims 23-24 is found throughout the specification. For example, page 23, lines 11-16, and page 24, lines 26-28, of the substitute specification filed 10/22/03, describe a construct of the invention having an IgG1 hinge. The amendment has been made for the purposes of expediting prosecution. The amendment includes no new matter.

II. The Rejection of Claims 23-44, 48, 102-106 and 142-148 under 35 U.S.C. §112, First Paragraph, Written Description, Should Be Withdrawn

The Examiner rejects claims 23-44, 48, 102-106 and 142-148 under 35 U.S.C. §112, first paragraph, as allegedly lacking written description, asserting that the specification does not describe a polypeptide having any IgG hinge region with an alternate number of cysteines, wherein the first cysteine that forms a disulfide bond is retained.

The claims as amended are directed to a single chain protein having a binding domain polypeptide, an IgG1 hinge region, and IgG CH2 and CH3 regions. The specification teaches methods of making polypeptides of the invention having IgG1 hinge regions based on naturally occurring IgG1 hinge regions, and teaches that the number of cysteines in the hinge region may be reduced, by either deletion or substitution of naturally-occurring cysteine residues (page 24, lines 15-19 and Example 5).

The specification describes that the hinge regions of the invention may be based on wild-type hinge regions, wherein the number of cysteine residues may be reduced by deletion or amino acid substitution. The present claims are directed to an IgG1 hinge in which the number of cysteines has been reduced, and the first cysteine in the IgG1 hinge which binds a light chain region has been retained. The specification describes both a wild-type IgG1 hinge and an IgG1 hinge in which the number of cysteines has been reduced, and discloses the location for the cysteines in the IgG1 hinge. One of ordinary skill in the art would readily understand that the number of cysteines can be "reduced" as stated in the application by either one or two or three residues using techniques well-known in the art, and would understand what is meant by the "first cysteine of the hinge that is responsible for forming a disulfide bond with a light chain constant region in a naturally occurring IgG antibody is not deleted or substituted."

What is well-known in the art need not be included in the application (See *Hybritech v Monoclonal Antibodies*, 802 F.2d 1367 (Fed. Cir. (1986)). Further, an adequate written description of the invention may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention. See, e.g., *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1323, 56 USPQ2d 1481, 1483 (Fed. Cir. 2000)) The present specification sets out the sequence of the IgG1 hinge, indicates that the number of cysteines can be reduced, and demonstrates methods for reducing the numbers of cysteines. As such, a worker of ordinary skill would know which residues in the IgG1 sequence could be altered as Applicants suggest, and would understand that Applicants were in possession of the present invention having an IgG1 hinge consisting of either one or two cysteine residues, wherein the first cysteine of the hinge is not deleted or substituted.

As such, applicants have described polypeptide of the invention having IgG1 hinge regions comprising either one or two cysteine residues, and the rejection of the claims under 35 USC §112, first paragraph, as lacking written description should be withdrawn.

III. The Rejection of Claims 23-44, 48, 102-106 and 142-148 under 35 U.S.C. §112, First Paragraph, Enablement, Should Be Withdrawn

The Examiner rejects claims 23-44, 48, 102-106 and 142-148 under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement, asserting that the specification does

not enable a polypeptide having any binding domain specificity and having CH2-CH3 regions based on any immunoglobulin polypeptide that also mediates ADCC. The examiner asserts that there is an art recognized lack of ADCC activity for IgA antibodies and for the lack of complement activation for all IgG (citing Tan et al , *Proc Natl Acad Sci USA* 87:162-166, 1990) antibodies, therefore one of ordinary skill in the art could not make and use the present invention. Applicants respectfully disagree.

The claims as amended are directed to single chain polypeptide having an hinge region based on an IgG1 antibody and CH2 and CH3 constant regions from an IgG antibody. The IgG1 hinge mediates both ADCC and CDC effector functions in IgG1 antibodies (Tan et al., *Proc Natl Acad Sci USA* 87:162-166, 1990). Further, Tan teaches that IgG antibodies which do not normally activate the complement cascade are capable of binding to complement proteins (Tan et al., *supra*, col. 1, p 165), and that it appears that the flexibility of the hinge plays a role in whether the antibody carries out CDC (Tan et al., *supra*, col. 2, p 165). The specification teaches how to generate an polypeptide of the invention having an IgG1 hinge and IgG CH2 and CH3 domains and teaches methods for measuring ADCC and CDC function of a polypeptide of the invention.

Additionally, the pending claims are commensurate with the evidence submitted in the declaration of Dr. Wahl (submitted March 21, 2007), describing constructs comprising IgG1 hinge regions based on the wild-type IgG1 hinge, which retain the first cysteine in the hinge region and carry out ADCC and CDC effector function. Therefore, one of ordinary skill in the art can readily make and use a construct according to the invention having an IgG1 hinge and IgG constant regions and that carries out both ADCC and for CDC activity.

The rejection of the claims under 35 U.S.C. §112, first paragraph, enablement, should therefore be withdrawn.

IV. The Rejection of Claims 23-44, 48, 102-106 and 142-148 under the Doctrine of Obviousness-Type Double Patenting Should Be Withdrawn

The examiner provisionally rejected pending claims 3-44, 48, 102-106 and 142-148 under the doctrine of obviousness-type double patenting in view of claims 1-53 of co-owned, co-pending application no. 11/088,693, and over claims 1-22 of co-owned, co-

pending application no. 10/207,655 in view of Shan (*J Immunol* 162:6589-95, 1999 (hereinafter "Shan") and Liu (*J. Immunol* 139:3521-26, 1987 (hereinafter "Liu")

Applicant acknowledges the Examiner's objection and will file any necessary terminal disclaimer(s) upon an indication that claimed subject matter is otherwise allowable.

V. Conclusion

Applicants respectfully submit that the claims are in condition for allowance and request early notification of same.

Dated: July 19, 2007

Respectfully submitted,

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